IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MEDPOINTE HEALTHCARE INC.,	)	
	)	
Plaintiff,	)	C.A. No. 06-164 (SLR)
	)	
v.	)	**PUBLIC VERSION**
	)	
APOTEX INC. and APOTEX CORP.,	)	
	)	
Defendants.	)	

APOTEX'S RESPONSE TO MEDPOINTE'S OPENING BRIEF ON CLAIM CONSTRUCTION ISSUES

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I. INTRODUCTION

Because claim construction presents a pure question of law, MedPointe's invitation to the Court to engage in factual inquiries and to use claim construction to compare claim scope to accused formulations or the prior art is improper. MedPointe's attempt to resolve factual issues before trial perverts the proper function of claim construction.

Moreover, because claim construction does not necessarily involve simply picking one proposal or the other, MedPointe's tactic of attempting to identify an extreme, unnatural reading of Apotex's proposed construction and then arguing that "for that reason alone, Apotex's proposed construction must be rejected", must itself be rejected. MedPointe's Opening Brief on Claim Construction Issues (D.I. 103) at pages 12, 16 and 17.

II. SPECIFIC RESPONSES

A. "Irritation or Disorders of the Nose and Eye".

If the applicant wanted to limit Claims 1–11 of the '194 patent (Ex. A) to "rhinitis" and "conjunctivitis", it was the applicant's obligation to use that language and those specific words, instead of using the readily understood and broader words "irritation or disorders." Apotex notes the patentee used two ***different*** phrases to define the scope of applicability for the claimed method of treatment in the two independent claims of the '194 patent. Claims 1–11 broadly encompass methods to treat "irritation or disorders of the nose and eye". Ex. A (col. 8, ll. 1-40). The method of claim 12, by contrast, is described as being limited to treatment of "allergy-related, or vasomotor or rhino-related colds or symptoms". Ex. A (col. 8, ll. 40-46). Now uncomfortable with the broad claim scope the applicant intentionally sought and obtained during prosecution, MedPointe attempts to use claim construction to rewrite the broad language it used in Claims 1–11 to mean something more akin to the narrower language of Claim 12. However,

the goal of claim construction is merely to define the metes and bounds of the subject matter of the claims, and re-writing the claims using language the remorseful patent owner now prefers is simply impermissible. It is equally axiomatic that the Court cannot rewrite the claims by importing and adopting limitations from the specification language different from the language the patentee used in the claims allowed to issue. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) ("[A]lthough the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments."); *accord, In re Trans Texas Holdings Corp.*, 498 F.3d 1290, 1299 (Fed. Cir. 2007) (observing that Courts can use the specification to understand the claims, but must not import limitations from the specification into the claims."); *Varco, L.P. v. Pason Systems USA Corp.*, 436 F.3d 1368, 1373 (Fed. Cir. 2006); *CollegeNet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 1231 (Fed. Cir. 2005) ("In examining the specification for proper context, however, this court will not at any time import limitations from the specification into the claims."); *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1374 (Fed. Cir. 2005) ("The specification makes numerous references to a preferred embodiment of the invention with three blades, . . . but that narrower embodiment does not impose a limit on the broader claim language as elucidated by the reference to "the invention" as embracing a 'plurality of blades.'"); *Leggett & Platt, Inc. v. Hickory Springs Mfg. Co.*, 285 F.3d 1353, 1357 (Fed. Cir. 2002) ("In consulting the specification, however, the interpretative process may not import limitations from the specification into the defining language of the claims."); *Comark Commc'ns v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998) (refusing to import limitations from the specification to the claims); *Sjolund v. Musland*, 847 F.2d 1573, 1581 (Fed. Cir. 1988) (same); *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 805 F.2d 1558, 1563 (Fed. Cir. 1986) ("This court has

cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification.").

In support of its limiting construction, MedPointe contends the specification does not discuss any irritation or disorders of the nose and eye other than rhinitis and conjunctivitis. MedPointe's Opening Brief on Claim Construction Issues (D.I. 103) at page 6. Apotex contends, as outlined in its opening brief, this element found in the non-limiting preamble of Claim 1 need not be interpreted, but even if it were limiting, the specification enumerates many diseases of the nose and eye beyond just rhinitis and conjunctivitis. Defendant's Initial Claim Construction Brief (D.I. 102) at pages 6-7. Furthermore, the examples and description in the '194 patent specification do not determine the scope of the subject matter claimed, but instead explain to those of ordinary skill in the art how to practice the claimed subject matter. *Johnson & Johnston Assocs. Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1052 (Fed. Cir. 2002) (*en banc*) ("Consistent with its scope definition and notice functions, the claim requirement presupposes that a patent applicant defines his invention in the claims, not in the specification. After all, the claims, not the specification, provide the measure of the patentee's right to exclude."); *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1121 n. 14 (Fed. Cir. 1985) ("Specifications teach. Claims claim."). For at least a century and a half, in utility patents it has been the claims, not the specification, that define the subject matter the applicant regards as his invention. Long, long ago this country abandoned the practice known as "central claiming", which permitted an applicant to claim an invention "substantially as shown and described" in the specification; that practice now survives only for design patents, not for utility patents such as the '194 patent. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 996 (Fed. Cir. 1995) (observing that the 1870 patent act codified a stated judicial preference for particularized claiming). Therefore, if

MedPointe wanted to limit Claims 1–11 to "rhinitis" and "conjunctivitis", it was MedPointe's obligation to use that language and those specific words in the claims it chose to write, instead of using the other words "disorders" and "irritations." Ex. A (col. 8, ll. 1-6).

Next, MedPointe not only would confuse the issue of law presented with questions of fact but wants this Court to rely on expert testimony in support of its peculiarly limiting construction of readily-understood words – despite strong warnings against applying expert testimony to this question of law. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1585 (Fed. Cir. 1996) citing *Markman v. Westview Instr.*, 52 F. 3d 967, 970-71 (Fed. Cir. 1995) *(en banc)*, *aff'd* 517 U.S. 370 (1996); *accord, Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298 (Fed. Cir. 2003). The testimony that MedPointe cites relates most to factual questions regarding the scope and content of the prior art and/or infringement, and not to the legal issue of whether the claimed method is limited in the way MedPointe argues. [redacted] This testimony shows that MedPointe is going beyond claim construction and encroaching on the factual question of comparing claim language to the prior art or to accused methods.

Not content with merely rewriting the claim, MedPointe also tries under the guise of claim construction to preempt factual inquiries by defining, as a matter of law, the symptoms of rhinitis. There is not one word in Claims 1–11 about rhinitis, let alone the ***symptoms*** of rhinitis. Defining the symptoms of a disease is clearly a factual inquiry, not a question of law and not an issue of claim construction. Moreover, the materials MedPointe cites confirm that this list is

exemplary, not limiting, ("characterized mainly by", MedPointe's Opening Brief on Claim Construction Issues, D.I. 103, Ex. F.) Contrary to MedPointe's position, factual controversies are the very stuff of trial and not "unnecessary disputes" to be "avoided". MedPointe's Opening Brief on Claim Construction Issues, D.I. 103 at 8.

Whether some treatment of a ***specific*** "irritation or disorder" of the nose and eye, "rhinitis," "conjunctivitis," or any other condition, is covered by Claim 1, or whether a particular reference treating, e.g., a condition other than "rhinitis" or "conjunctivitis" is pertinent prior art, poses a factual question best resolved at trial in light of the particular reference. It should not be dealt with as a matter of claim construction by replacing the words "disorder" and "irritation" with narrower, more specific terminology MedPointe now wishes the applicant had used.

B. "Applying Directly To Nasal Tissues Or The Conjunctival Sac Of The Eyes".

Again, MedPointe invites the Court to go beyond simple claim construction and to compare the claim language to the prior art, a question of fact presented by anticipation and subsidiary to the determination of obviousness. In asking the Court to rule that the claim language "[e]xcludes oral and parenteral applications" (MedPointe's Opening Brief on Claim Construction, D.I. 103 at 10), MedPointe is ***not*** elucidating what the words mean but instead urges the Court to compare the claim language to these specific methodologies to determine if they are covered. Whether any particular oral or parenteral application is pertinent prior art and whether it anticipates is a factual question best determined in the context of, and with reference to, that particular prior art reference, not in the abstract. That is the reason for having a trial and receiving evidence, including the prior art references that Apotex contends invalidate the patent in suit.

It is well established that a determination of infringement is a two step process. The first step, claim construction, is a question of law while the second step, comparison to the accused product, is a question of fact. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996) (citations omitted); *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998) (*en banc*). So, too, anticipation requires both claim construction, a question of law, and comparison of the claim language to the prior art, which comparison presents a question of fact. *Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998) ("We observe in passing that, not unlike a determination of infringement, a determination of anticipation, as well as obviousness, involves two steps. First is construing the claim, a question of law for the court, followed by, in the case of anticipation or obviousness, a comparison of the construed claim to the prior art. This comparison process involves fact-finding, and is for the fact-finder in the first instance."); *Beachcombers v. WildeWood Creative Prods., Inc.*, 31 F.3d 1154, 1163 (Fed. Cir. 1994) ("As with the validity question, a determination of patent infringement is a two-step analysis.").

Replacing the phrase "applying directly" in Claims 1–11 with the phase "topical application" does nothing to construe those claims. If anything, the proposed language is more technical and more esoteric, not less. It also raises more questions than it answers, such as whether, e.g., transdermal patches or the like which are applied "topically" would be encompassed within MedPointe's claim construction. ***That*** question (a question of fact), however, is not whether such routes of administration are "topical" but instead whether they amount to "applying directly", as Apotex proposes. MedPointe's definition of "topical application" should therefore be rejected as meaningless surplusage. Claim construction does not require the court to rewrite terms that are already written in plain English. *U.S. Surgical*

Corp. v. Ethicon, Inc., 103 F.3d 1554, 1568 (Fed. Cir. 1997) ("Claim construction is a matter of resolution of disputed meanings and technical scope, to clarify and ***when necessary*** to explain what the patentee covered by the claims, for use in the determination of infringement. It is not an obligatory exercise in redundancy.") (emphasis added).

C. "A Member Selected From The Group Consisting Of Azelastine And Its Physiologically Acceptable Salts".

MedPointe proposes to use the phrase "a member selected from the group consisting of azelastine and its physiologically acceptable salts" to import limitations concerning safety, efficacy, and tolerability, and to limit the claim to human use, excluding veterinary application. The term "physiologically acceptable" does not mean anything of the sort, and the rest of the claim does not support that strained interpretation.[1] Again, if the patentee intended to ***define the invention*** by these properties, it was obliged to recite those concepts ***in its claim*** or to clearly define extant claim term(s) in the specification so such unconventional lexicography would be clear to the person having ordinary skill in the art. *Phillips*, 415 F.3d at 1316.

First, the claim language itself simply does not mention safety, efficacy, or tolerability. It is the claims that define the scope of the invention, and the patent-in-suit is not a method defined by the elements of safety, efficacy, and tolerability. The patent-in-suit, by contrast, claims a "method … which comprises applying directly to nasal tissues or to the conjunctival sac of the eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts." Ex. A (col. 8, ll. 1-6).

1 [redacted]

Moreover, the unclaimed elements "safety" and "efficacy" are the particular bailiwick of the Food and Drug Administration ("FDA"), not of the United States Patent and Trademark Office ("USPTO"). The USPTO is neither equipped, nor competent to determine whether claimed subject matter is safe and effective. The FDA, not the USPTO, is exclusively charged with that task.

Obviously, MedPointe will have at its disposal a tremendous amount of material relating to safety and efficacy in human usage of one particular formulation and dosage, the formulation and dosage it was approved to sell. It had to generate that information in order to prove safety and efficacy to the satisfaction of the FDA. That proof, however, was neither required by the statute to establish patentability nor can it become a claim limitation now merely because the FDA eventually approved MedPointe's product.

The undisputed facts prove the point. The '194 patent issued November 17, 1992. Not until November 1, 1996, did the FDA conclude that use of the brand-name pharmaceutical allegedly covered by this patent was safe and effective. Under MedPointe's strained claim interpretation, one could not know whether use of MedPointe's own product was covered by the patent-in-suit until after the FDA ruled on its application, years after the patent issued. Furthermore, evidence of the safety and efficacy of a single formulation and dosage cannot be used now to support the claim construction regarding the safety and efficacy of an almost unlimited number of formulation and dosage combinations that are claimed. Safety, efficacy, and tolerability were not elements of the claims in 1992 and cannot be imported now.

Moroever, proof of safety, efficacy, and tolerability could not distinguish over the prior art because the degree that any particular formulation or dosage is safe, efficacious, and tolerable is an inherent property of that formulation or dosage administered by the claimed method. If the

prior art discloses any topical application of azelastine, otherwise within the scope of the claims, it does not matter whether anyone appreciated the alleged safety, efficacy, and tolerability of that method at the time. *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("Other precedents of this court have held that inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure."); *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005) ("Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claims limitations, it anticipates.""); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002); *MEHL/Biophile Int'l Corp. v. Milgraum,* 192 F.3d 1362, 1365 (Fed. Cir. 1999).

Not only is MedPointe's interpretation improper as a matter of law, it simply does not follow as a matter of logic from the materials MedPointe cites in support. Even if the specification asserts that azelastine is "a well tolerated and improved remedy", that phrase is not tied in any way to the term "physiologically acceptable." Ex. A (col. 2, ll. 3-4). It is certainly not a definition of that term. Even if it were permissible to import the "well tolerated" and "improved remedy" from the specification to the claims as limitations (and it is not), MedPointe does not stop there but goes on to assert, without support, that "improved remedy" means safety and efficacy and that "well tolerated" means tolerability (an undefined term).

Importantly, MedPointe never defines safe, efficacious or tolerable. If MedPointe intends "tolerable" to mean acceptable to human patients (although there is no support for such a definition in the specification, much less the claims), then by the inventor's own admission, formulations and dosages within even the narrowest dosage ranges of claim 4 are not enabled.

[redacted]

[redacted] In fact, if this Court were to adopt MedPointe's claim construction, another round of claim construction would be required to define what exactly safe, efficacious and tolerable mean. MedPointe's position does not relate to claim construction. It relates to fabrication of new, unsupported, and undefined claim elements out of whole cloth based on FDA approval four years after the patent issued and nine years after the effective priority date of November 13, 1987.

MedPointe's insistence that the claims are limited to human use, and exclude veterinary use, similarly has no support. While humans are the subject of the particular products accused of infringement, it has nothing to do with the scope of the patent. The patent nowhere uses the words "human" or "person". The deposition testimony MedPointe cites also does not support that conclusion. [redacted]

[2] The parties are still wating for the official transcript of the German proceedings from the German court, and Apotex requests leave to supplement the record with a direct quotation once an official transcript is available.

[redacted] "Physiologically acceptable" could apply to humans subjects ***or*** to animals, and here merely denotes a salt form that may be administered by any route.

While considering this term, it should also be noted that the patentee also chose to recite this claim element in the linguistic structure referred to in patent law as a "Markush" group, a recitation of a finite number of enumerated alternative elements which has the form "a member selected from the group consisting of . . .". This language is significant because it excludes combinations of the free base and salt forms, and perhaps even of different salt forms within the same application, because the claim says that the medicament contains a member of the group consisting of azelastine and its physiologically acceptable salts. *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1281 (Fed. Cir. 2003) ("Thus, the plain meaning of asserted claims 1 and 6 limits them to a single Lewis acid inhibitor selected from the recited Markush group, and present in an amount effective to prevent degradation of sevoflurane by Lewis acids.").

While the Markush group uses the closed form "consisting of", the claim as a whole uses the open form transitional phrase "comprising", which means "including but not limited to." *Vehicular Techs. Corp. v. Titan Wheel Int'l*, 212 F.3d 1377, 1382 (Fed. Cir. 2000) ("The phrase 'consisting of' is a term of art in patent law signifying restriction and exclusion, while, in contrast, the term 'comprising' indicates an open-ended construction.") (citation omitted). Similarly, the term "containing" that the patentee used to introduce the constituent parts of the medicament is considered an "open" term which means "including but not limited to" and permits other ingredients to be included. *Mars, Inc. v. H.J. Heinz Co., L.P.*, 377 F.3d 1369, 1375 (Fed. Cir. 2004) ("We hold that neither term requires that the ingredients be limited only to

those ingredients listed in the claim itself. In other words, like the term "comprising," the terms "containing" and "mixture" are open-ended."). This means that the medicament recited can include ingredients (active or inert) other than azelastine or its salts, but cannot include a mixture of the free base and a salt. *See*, *Maxma v. ConocoPhillips, Inc.*, 2005 WL 1690611, at *5 (E.D. Tex. 2005) ("Properly viewed, the transitional phrase 'consisting of' closes the *group of alternatives,* not the claim.").

D. "A Medicament".

Concerning the term "medicament" which appears in all the claims 1–12, the MedPointe again seeks to import the extraneous concepts of safety, efficacy, and tolerability. Again, as with "physiologically", nothing in the claim language supports this strained interpretation. Instead, those concepts are relevant to FDA approval. MedPointe wants to make this case about those issues because it has evidence about safety, efficacy, and the like, which it developed in order to obtain FDA approval. But for that research, MedPointe already has its reward, which was FDA approval. The question of the validity of its patent is something else entirely. A medicament may (or may not) be patentable without regard to whether it is "safe and effective" so as to receive FDA approval, and vice versa a medicament may be "safe and effective" so as to receive FDA approval without regard to whether it is novel and non-obvious so a to merit a patent.

The term "medicament" really means nothing more than a thing intended to be used as a medicine. Maybe it is good medicine. Maybe it is bad medicine. Both are just different kinds of medicines, that is, medicaments. The most bizarre folk-remedy poultice ever used as a medicine was a medicament, although it may not have been be a very good one. Applying more modern standards, maybe a particular medicaments efficacy for what it treats outweighs any safety risks; maybe it does not. What makes it a "medicament," however is its intended usage, not how well it works or does not for that purpose.

[redacted]

MedPointe's criticism of Apotex's proposed claim construction is similarly without merit. MedPointe notes that under Apotex's proposed construction a "medicament" need not contain any active ingredient, but this argument is a red herring. In point of fact, a placebo can be a medicament, but it would not be covered by this claim because the claim requires among other things that the medicament contain Azelastine. The requirement for an active ingredient is not part of the inherent meaning of the term medicament, neither is that interpretation required for construing this claim because the claim itself specifies the active ingredient requirement using other language.

Moreover, even if medicament ***were*** construed to require the presence of some active ingredient, that would not support MedPointe's additional contention importing extraneous limitations of safety, efficacy, and tolerability. The term "medicament" is not unique to patent law; neither is it a technical term of art. In other cases construing the tariff laws, the Federal Circuit has distinguished between "medicaments" and "confectionaries" based on whether the product is intended "for therapeutic or prophylactic uses". *Warner-Lambert Co. v. U.S.*, 425 F.3d 1381, 1383 (Fed. Cir. 2005). Patent cases involving claims using the term "medicament" have not imported extraneous limitations about safety, efficacy, and tolerability. *E.g.*, *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001); *Merck & Co., Inc. v. Mylan Pharms., Inc.*, 190 F.3d 1335, 1338 (Fed. Cir. 1999).

MedPointe criticizes Apotex for supposedly offering a different definition of medicament in Claim 9 than in other claims, yet MedPointe then goes on to argue that the term "medicament" must be limited to the aqueous solution form supposedly usable in claim 9. MedPointe cites as support the description of the preferred embodiment, but it would be error to limit the claims to the preferred embodiment of described in the specification. If other forms of medicaments can be "applied by spraying", those other forms could also be covered by Claim 9. There is no reason to adopt MedPointe's stilted definition of the term "medicament" in order to reach this result. If some forms of medicaments cannot be "applied by spraying", then those forms simply are not covered by claims including that additional language. That is the reason for including such additional language. MedPointe's proposed claim construction methodology would make such language in dependent claims redundant by incorporating the limitations into the broader terms used in independent claims, which is directly contrary to the doctrine of claim differentiation.

Also in the context of the term "medicament", MedPointe introduces the assertion that the claims do not cover a method that also includes other active ingredients. That is simply a misconstruction of the terms "comprising" and "containing", which are open. *Mars, Inc. v. H.J. Heinz Co., L.P.*, 377 F.3d 1369, 1375 (Fed. Cir. 2004) ("[L]ike the term 'comprising,' the terms 'containing' and 'mixture' are open-ended."). To be covered by the claims a method cannot mix the free base and salt forms, but it can include other active ingredients.

E. "The Medicament Contains 0.003 To 0.5% (Weight/Weight) Of Azelastine Or An Amount Of A Physiologically Acceptable Salt Of Azelastine Which Contains 0.003 To 0.5% (Weight/Weight) Azelastine."

MedPointe astutely observes that that "there is no dispute regarding the dosage in Apotex's aqueous solution product". However, the absence of dispute on the characteristics of Apotex's proposed product, an issue of fact, does not mean that "this issue is appropriate for

resolution as a matter of claim construction." Claim construction is a matter of law, and it is not appropriate to insert new language for terms that are undisputed. *NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1311 (Fed. Cir. 2005) ("RIM's principal justification for this court to construe the "additional processor" limitation is simply that the district court below construed the claim term. That is not a sufficient basis for this court to construe this claim term. Terms not used in claims in controversy on appeal need not be construed.").

The question of what weight/volume percentage corresponds to the stated weight/weight percentage poses a question of fact. If the parties can reach agreement on that factual question then it can appropriately be included as a statement of uncontested fact in the pretrial order. If the parties cannot agree then the parties can state their positions in their respective statements of disputed facts. In either situation, however, whether or not the parties agree about this fact, it is clearly not a matter of claim construction. This is not a definition of the recited claim language, and should not be addressed as a matter of claim construction.

F. "Aqueous Solution".

A ***solution*** requires not only a ***solvent***, but also a ***solute***. In the aqueous solution of Claim 7, the solvent is water. The solute is something mixed in with the water, which could be one or more excipients, preservatives, or active ingredients. MedPointe asserts that the plain meaning of aqueous solution "does not require the addition of excipients, preservatives, or active ingredients." MedPointe Br. at 21. However, ***something*** has to be added the solvent (water), or else it is not a solution at all, it is just plain water.

MedPointe also apparently contends that the term "aqueous solution" must be construed to restrict the compound to a single active ingredient. Nothing about the term "aqueous solution" suggests such an interpretation. A solution can have one solute. It can have more than one solute. Clearly this claim is intended to encompass more than one solute, because it can include

at least an active ingredient and inactive ingredients; otherwise, it would cover neither the accused method nor MedPointe's own method.

Nothing in the ordinary meaning of "aqueous solution" restricts the claim to only one active ingredient. The patentee expressly provided for the claims to cover azelastine in combination with other active ingredients by using the open transition term "comprising" and the equally open term "containing", which are terms of art in patent law that mean "including but not limited to." *Mars, Inc.*, 377 F.3d at 1375. The patentee did use the closed transitional phrase "consisting of" in its Markush group, but that only prohibits combining the members of the Markush group with each other. It does not prohibit combining its members with other ingredients, active or inert. Indeed, if that phrase were construed to prohibit other active ingredients it would equally prohibit other inactive ingredients also, and therefore not cover either MedPointe's brand name pharmaceutical or Apotex's proposed generic. It does not matter whether the patent specification described the combination of azelastine with other active compounds because the specification is not intended to delineate the scope of the claims. The specification instructed one of ordinary skill in the art how to use at least one particular embodiment covered by the claims, but other embodiments not described (including the combination of azelastine with other active or inactive ingredients) are also within the claims' scopes.

MedPointe's invocation of the doctrine of claim differentiation is misplaced. First, Claim 5 includes limitations other than a preservative, such as specific ranges, and therefore would not in any sense be rendered superfluous. Claim 5 and Claim 6 both depend from Claim 1, so it is clear that the "medicament" of Claim 1 can include a "pharmaceutically acceptable preservative". Absolutely nothing in the plain meaning of the term "aqueous solution" precludes

this form of the medicament from including such a preservative. Moreover, Claim 5 and Claim 6 are still of markedly different scope because Claim 5 would encompass cover medicaments including a preservative in the specified range regardless of whether it is in a solution, and Claim 6 would cover a medicament in solution regardless of whether it includes a preservative.

G. "Solution".

MedPointe's proposed construction of the term "solution" suffers from the same defect as its proposed construction of the related term "aqueous solution". Clearly the claims will only cover a method that includes the use of azelastine, but the patentee drafted the claims in open, not closed, form, so the combination of azelastine with other ingredients would still be covered. It does not matter whether those ingredients are active or not. Nothing in the word "solution" prohibits the mixture of additional solutes.

There is also nothing whatsoever in the word "solution" that requires that the mixture be safe, effective, and tolerable, as MedPointe urges. Even if those characteristics were required by the word "medicament" (and they are not, as explained above in construing that term), that would be a basis for construing the word medicament, not the word solution. A solution may be safe or unsafe, but it is still a solution. Whether or not that solution falls within the ambit of the rest of the claim language is another question, and not a matter of construing the word solution.

H. "Applied By Spraying".

As with other disputed claim terms, legal question of construing the term "applied by spraying" is very different from the factual questions of comparing this language to any particular spray, mist, aerosol, atomizer, shower, jet, squirt, spew, pump, fog, haze, or vapor. MedPointe asks the court to determine ***as a matter of law*** that if the volume applied by spraying is less than 50 microliters or more than 150 microliters then it is not really "applied by spraying". MedPointe also asks the court to rule ***as a matter of law*** that if that which is applied by spraying

has droplets smaller then 10 micrometers or bigger than 250 micrometers then it is not really "applied by spraying."

MedPointe's argument simply does not concern a question of law. It is not even question of claim construction. Instead, it involves comparison of the claim language "applied by spraying" to a particular example, having particular measured amounts. Such a comparison is a factual inquiry (whether determining infringement or anticipation), and should only be resolved based on evidence about what the relevant parameters are and whether or not it is applied by spraying.

Similarly, MedPointe's factual assertion that particles of a certain size would be so small as to reach the lungs is not a matter of claim construction. It is a factual question of comparing the claim language to a particular embodiment. If the spray is applied to nasal tissues or to the conjunctival sac of the eyes, it does not matter is some of the spray also lands on other places.

It may well be that particular embodiments and examples in the specification fall within the ranges MedPointe suggests, but that does not mean that the claims are limited to those ranges. It does not even reasonably suggest that the claims should be limited. Examples are just that, examples. It may be useful for illustrating one specific factual milieu that, upon factual comparison, is covered by the phrase "applied by spraying", but it does not in any sense define that term.

There is also nothing in the term "applied by spraying" which excludes from the scope of that language application to the eyes. Now it could be that in fact, as a practical matter, no one every applies by spraying to the eyes, but if so then that is a ***factual*** question. It is not a matter of claim construction, and there is no reason for the court to try to answer that as a question of law.

MedPointe also contends that claim differentiation supports its interpretation of Claim 9. It does not. It is perfect permissible and even expected that Claims 9, 10, and 11 would overlap in their scopes. Different words generally have different meanings, but those meanings can and often do overlap.

In Claim 9 the medicament "is applied by spraying."

In Claim 10 the medicament "is applied as drops."

In Claim 11 the medicament "is a powder."

The first of these three concerns the manner in which the medicament is applied, the second concerns the form when it is applied, and the third concerns the form at any time. Some particular drops may in fact be included in a spray and covered by both claims 9 and 10. Some particular drops may in fact ***not*** be a spray, and therefore covered by Claim 10 but not Claim 9. Some particular powder might in fact be applied by spraying the powder on the affected area. Such method would be covered by Claim 11 and Claim 9, but not by Claim 10 because it would not include drops. Other powders may be sprinkled on the affected area and therefore covered by the method in Claim 11 but not the method in Claim 9 or Claim 10. As these examples make clear, these claims have different scopes associated with their different words, even if those scopes may overlap. The question of whether any one of these claims covers any particular embodiment is a question of fact, not of claim construction.

This would not be the first patent in which particles could be "applied by spraying." The case *In re Peterson*, 189 F.2d 288, 290 (C.C.P.A. 1951) concerned "finely divided particles of electrically conductive materials such as flake metal particles in a suitable bonding medium" which could be "applied by spraying or the like." *Id.* Neither drops nor droplets were necessary, merely "finely divided particles", i.e., a powder.

III. CONCLUSION

Wherefore, for the reasons stated, Apotex respectfully requests that the Court reject the legally incorrect claim constructions urged by MedPointe and instead construe the claim as explained by Apotex in its initial brief on claim construction (D.I. 102).

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842210 / 30136

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

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EXHIBIT A

US005164194A

United States Patent [19]

Hettche

[11] Patent Number: 5,164,194

[45] Date of Patent: Nov. 17, 1992

[54] **AZELASTINE CONTAINING MEDICAMENTS**

[75] Inventor: **Helmut Hettche**, Dietzenbach, Fed. Rep. of Germany

[73] Assignee: **Asta Pharma AG**, Fed. Rep. of Germany

[21] Appl. No.: **551,644**

[22] Filed: **Jul. 12, 1990**

Related U.S. Application Data

[63] Continuation of Ser. No. 268,772, Nov. 9, 1988, abandoned.

[30] **Foreign Application Priority Data**

Nov. 13, 1987 [DE] Fed. Rep. of Germany 3738681

[51] **Int. Cl.**[5] **A61K 9/14**; A61K 31/55

[52] **U.S. Cl.** **424/489**; 424/43; 424/45; 424/464; 424/422; 514/212

[58] **Field of Search** 424/43, 464, 422, 45, 424/489; 514/212; 222/394; 141/24; 239/302; 248/108

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[57] **ABSTRACT**

A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt.

12 Claims, No Drawings

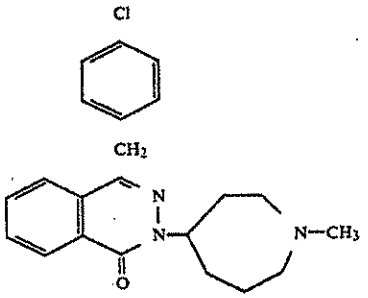
AZELASTINE CONTAINING MEDICAMENTS

This is a continuation of application Ser. No. 07/268,72, filed Nov. 9, 1988, now abandoned.

The present invention relates to the treatment of nasal and eye tissues with azelastine.

BACKGROUND OF THE INVENTION

Azelastine is a phthalazinone derivative having the following structural formula:



The chemical designation is: 4-(4-chlorobenzyl)-2-(perhydro-1-methyl-azepine-4-yl)-1-(2H)phthalazinone. Azelastine is used in particular for prophylactic treatment of asthma. Azelastine also has anti-allergic and antihistamine properties, see German Patent No. 21 64 058.

SUMMARY OF THE INVENTION

It has now been found that azelastine and its physiologically acceptable salts display particularly advantageous and surprising effects when the corresponding formulations are applied directly in the nose and/or to the conjunctival sac of the eye.

Elimination or marked relief has thus been achieved not only in allergy-related rhinitis, but also in the normal common cold (caused, for example, by rhino viruses) as well as in the vasomotor cold and the symptoms of illness triggered thereby.

It is surprising in this context that local nasal application also has a favorable effect on the mucous membrane of the eye (elimination or relief of reddening of the eye and of eye irritation) so that the additional use of eye drops is frequently superfluous.

Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza.

Surprisingly, in addition, none of the tiredness that arises with other applications was observed with use according to the invention.

Furthermore the invention provides a way to overcome problems which arise because of azelastine's exceptionally penetrating, bitter taste. The degree of the bitter taste is so intense that it is even found to be unpleasant in a dilution of 1 : 706. This problem has hitherto prevented oral application of azelastine solutions, since patients refuse to take such azelastine solutions or suspensions. It wa surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose. As a result, it is possible in this manner to apply solutions or suspensions of azelastine and its salts nasally without taste impairment. Moreover the bitter taste is barely perceptible when the sprayed azelastine solution or suspension runs down into the pharynx.

Therefore, the object of the present invention is to provide a well tolerated and improved remedy based on azelastine or its salts for the treatment both of the allergy-related and vasomotor-related conditions as well as rhino virus-related cold and its accompanying symptoms.

A further object of the present invention is to provide medical formulations which are adapted to direct application to nasal and eye tissues.

The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used in the form of drops, ointments, creams, gels, insufflatable powders or, in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. For example 0.03 to 3 mg of azelastine base should be released per individual actuation.

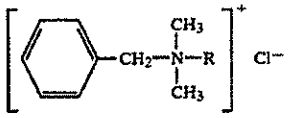
Through the use of nasal drops or a nasal spray, the dosage of azelastine required for the treatment of the cold is lowered approximately tenfold and hence the incidence of the appearance of side effects is considerably lower than in the case of the application of azelastine in orally taken dosage forms such as tablets or syrups which distribute the active substance throughout the entire body. In the treatment of a banal illness such as a cold, a low incidence of side effects is particularly important and thus represents a considerable medical advance.

Solvents which may preferably be used for the formulations of the invention are: water, saturated aliphatic mono and polyvalent alcohols which contain 2-3 carbon atoms (for example ethanol, isopropanol, 1,2-propylene glycol, glycerine), liquid polyglycols (molecular weight 200 to 600).

The solvent used is preferably water or mixtures of water with other physiologically acceptable solvents (for example those mentioned above). Preferably, the amount of the latter solvent in the aqueous mixture should not exceed 15% by weight.

The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore, it is possible, for example, to use sodium-(2- ethylmercurithio)-benzoate generally known as "thimerosal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01% (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl- butyl)]phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-:-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preserva-

tives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride". These latter consist of a mixture of the compounds of formula,



in which R represents an alkyl group having the formula C_nH_{2n+1}, wherein n represents a whole number from 8 to 18. The use of a mixture of compounds in which n represents 10 to 14 is particularly preferred and in particular the special compound in which $R=C_{12}H_{25}$ "Benzalkonium chloride" and the compounds of the above formula can be used in concentrations of 0.005 to 0.10, preferably of 0.005 to 0.05, for example of 0.01% (weight/volume for liquid formulations, otherwise weight/weight) and they may optionally be used in combination with 0.2 to 2.0, for example 0.4% (weight/ volume) of 2-phenylethanol.

The formulations of the invention (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) contain 0.0005 to 2, preferably 0.001 to 1, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should the azelastine be present as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine itself mentioned above. In the case of the eye drops, the same azelastine concentrations apply as in the case of the nasal forms.

In the case of powders, the concentration of azelastine base is 0.0005 to 2 percent by weight related to the solid carrier substances.

In the case of solutions, the dosage per nostril is, for example, 0.01 to 0.2 ml, in particular 0.05 to 0.15 ml. Such a dosage should be applied once to several times, preferably 1 to 5 times daily (optionally also hourly).

In the case of use at the eye (eye drops) the dosage is for example 1 drop (about 0.05 ml) of the solution or corresponding amounts of the semi-solid formulation forms.

Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr), sulphuric acid, phosphoric acids (H_3PO_4, metaphosphoric acid, polyphosphoric acids), nitric acid, organic mono-, di- or tricarboxylic acids of aliphatic, alicyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is between 0.001 to 0.10, preferably 0.01 g per 100 ml of solution/suspension or 100 g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used:

thimero sal 0.002–0.02%;

benzalkonium chlorie 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;);

chlorhexidine acetate or gluconate 0.01 to 0.02%;

phenyl mercuric/nitrate, borate, acetate 0.002–0.004%;

p-hydroxybenzoic acid ester (for example a mixture of the methyl ester and propyl ester 7 : 3): 0.05–0.15, preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is used in a concentration of 0.05 to 0.1%, benzalkonium chloride being used in a concentration of 0.005 to 0.05%, preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/-weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerization of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine components.

In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50° to 0.56° C. is attained in comparison to pure water. In Example 1, for instance, such substances would be used in such an amount which is iso-osmotic with 68 g of sodium chloride (0.68%).

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example:

Glucose $1H_2O$ 3.81 g ; saccharose 6.35 g ; glycerine 2.2 g; 1,2-propylene glycol 1.617 g ; sorbitol 3.84 g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.s. Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight are, for example, used for this purpose.

It is also possible to add to the formulations buffer substances such as citric acid / sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 6 to 7.5, preferably 6.5 to 7.1.

The amount of citric acid is, for example, 0.01 to 0.14, preferably 0.04 to 0.05 g, the amount of disodium hydrogenphosphate 0.1 to 0.5, preferably 0.2 to 0.3 g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer should be less than 5%, in particular less than 2% (weight-/volume).

For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in the form of a solution or suspension in a so-called propellant. Propellants are pressurized liquid chlorinated, fluorinated hydrocarbons or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutane or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed into the nose or which are available for inspiration into the nose. Certain plastic applicators are used to actuate the valve and to convey the sprayed suspension into the nose. Propellants that may, however, also be used are: CO_2, nitrous oxide and compressed air.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

When suspensions are used, the maximum particle size of the solid substances (azelastine +auxiliary substances) should not exceed 30 μm.

In the case of use in the form of an insufflatable powder, the maximum particle size of the substances should not be greater than 20 μm.

What occurs is, for example, a vaporizing of solid azelastine or its salts. In this case the azelastine or its salt is, for example, mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate. The concentration of azelastine is 1 part by weight of azelastine to 50 to 200,000 parts by weight of carrier substance (0.0005 to 2% of azelastine).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is illustrated by the following examples.

EXAMPLE 1

Nasal spray or nasal drops or eye drops with 0.1% azelastine hydrochloride as active ingredient

The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride, 5 g of edetic acid disodium salt. 2 H_2O, 68 g of sodium chloride, 1.25 g of alkyl-benzyldimethylammonium chloride (benzalkonium chloride), 4.38 g of citric acid, 64.8 g of sodium monohydrogen-phosphate. 12 H_2O as well as 10 g of hydroxypropylmethyl cellulose.)[1]

[1] Commercially available product, for example methocel E4M premium.

The solution obtained is diluted to 10.05 kg = 10 liters with water. The solution is filtered through a membrane filter of pore size 0.2 μm after careful mixing, the first 500 ml of filtrate being discarded. The filtrate has a pH value of 6.8 ±0.3. This is filled into plastic bottles which are closed with a conventional spray insert or into plastic or glass bottles which are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example used, which spray about 0.14 ml of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride are sprayed into the nose per actuation in the form of the solution.

If the above obtained filtrate is filled into the bottles with dropper pipettes conventionally used for nasal drops or eye drops, the solution can be dripped into the nose or eye using a dropper pipette.

EXAMPLE 2

Nasal ointment with 0.1% of azelastine hydrochloride

5 kg of polyoxyethylene stearate[2], 8 kg of cetylstearyl alcohol (Lanette 0), 20 kg of white Vaseline, 15 kg of liquid paraffin and 0.5 kg of silicon oil are melted together in a heatable vessel. 126 g of p-hydroxybenzoic acid methyl ester and 53 g of p-hydroxybenzoic acid propyl ester are dissolved in the melt (temperature of the melt 80° C.). Subsequently, a solution heated to 70° C. of 0.1 kg of azelastine hydrochloride, 140 g of p-hydroxybenzoic acid methyl ester and 60 g of p-hydroxybenzoic acid propyl ester in 51.021 kg of purified water are emulsified with the aid of a high speed stirrer and the emulsion obtained is stirred until cold and repeatedly homogenized at regular time intervals.

[2] Polyoxyethylene-40-stearate, solid, white to cream-colored mass, $D.^{25}$ ca. 1.1, F. 40°–44° C. Solidification point ca. 41° C.

The ointment is filled into tubes which have a tubular extension beyond the thread and are thus particularly suitable for applying the ointment into the nose.

EXAMPLE 3

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride per stroke

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about −55° C. in an appropriate cooling vessel. A mixture of 0.086 kg of precooled sorbitantrioleate and 0.8600 kg of precooled trichlorofluoromethane are dissolved with stirring into this mixture at −55° C. 0.0688 kg of micronized azelastine hydrochloride and 0.0688 kg of micron-

ized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about −55° C.

Following closure of the cooling vessel the suspension is again cooled to about −55° C. under intensive stirring. It is then ready to be filled.

With continued stirring the suspension is filled into the conventional suitable aluminum monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 0.5 mg of azelastine hydrochloride. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

EXAMPLE 4

Eye drops with 0.05% of azelastine hydrochloride

140 g of polyvinylalcohol (trade name for example: Mowiol 26–88 / Hoechst AG, Frankfurt 80) are stirred into 4 liters of cold water for injection purposes, the suspension is heated to 90° C. and left at this temperature for 45 minutes. After cooling, the solution obtained is mixed with the following solutions:

5 g of azelastine hydrochloride in 1 liter of water for injection purposes, 0.2 g of phenyl mercuric nitrate in 2 liters of water for injection purposes, 70 g of sodium chloride in 1 liter of water for injection purposes.

The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide solution, mixed with a solution of 15 g of sodium dihydrogen phosphate.2 H_2O and 21 g of disodium hydrogen phosphate.2 H_2O in 1 liter of water for injection purposes and filled up to 10 liters with water for injection purposes.

Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 μm with glass fiber pre-filter and filled into sterile eye drop bottles under aseptic conditions after discarding a first 500 ml of filtrate.

What is claimed is:

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/-weight) azelastine.

3. A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim 1 in which the medicament is a solution.

7. A method as set forth in claim 1 in which the medicament is an aqueous solution.

8. A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim 1 in which the medicament is applied by spraying.

10. A method as set forth in claim 1 in which the medicament is applied as drops.

11. A method as set forth in claim 1 in which the medicament is a powder.

12. A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

* * * * *

ized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about −55° C.

Following closure of the cooling vessel the suspension is again cooled to about −55° C. under intensive stirring. It is then ready to be filled.

With continued stirring the suspension is filled into the conventional suitable aluminum monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 0.5 mg of azelastine hydrochloride. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

EXAMPLE 4

Eye drops with 0.05% of azelastine hydrochloride

140 g of polyvinylalcohol (trade name for example: Mowiol 26–88 / Hoechst AG, Frankfurt 80) are stirred into 4 liters of cold water for injection purposes, the suspension is heated to 90° C. and left at this temperature for 45 minutes. After cooling, the solution obtained is mixed with the following solutions:

5 g of azelastine hydrochloride in 1 liter of water for injection purposes, 0.2 g of phenyl mercuric nitrate in 2 liters of water for injection purposes, 70 g of sodium chloride in 1 liter of water for injection purposes.

The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide solution, mixed with a solution of 15 g of sodium dihydrogen phosphate.2 H_2O and 21 g of disodium hydrogen phosphate.2 H_2O in 1 liter of water for injection purposes and filled up to 10 liters with water for injection purposes.

Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 μm with glass fiber pre-filter and filled into sterile eye drop bottles under aseptic conditions after discarding a first 500 ml of filtrate.

What is claimed is:

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/weight) azelastine.

3. A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim 1 in which the medicament is a solution.

7. A method as set forth in claim 1 in which the medicament is an aqueous solution.

8. A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim 1 in which the medicament is applied by spraying.

10. A method as set forth in claim 1 in which the medicament is applied as drops.

11. A method as set forth in claim 1 in which the medicament is a powder.

12. A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

PATENT NO.	:	5,164,194
ISSUED	:	November 17, 1992
INVENTOR(S)	:	Helmut Hettche
PATENT OWNER	:	Asta Medica, AG

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

349 days

from November 17, 2009, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 27th day of February 1998.

Bruce A. Lehman

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and

EXHIBIT B

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT C

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT D

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EXHIBIT E

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EXHIBIT F

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EXHIBIT G

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